

Effects of pamidronate use on the palliative radiotherapy of bone metastases

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To analyze the impact of pamidronate (P) use on results of the palliative radiation treatment (RT) of bone metastases, 47 patients with bone metastases were treated with P+RT (19 patients) or RT alone (27 patients). RT was delivered with a standard scheme (10x3 Gy). 90 mg monthly-infusions of P, which started from the first day of RT and continued up to 9 months, were given in the P+RT group. After 24 weeks of follow-up, changes in the pain scores, quality of life index, ALP, tumor marker and Bone Mineral Density levels of whole skeleton significantly improved from base line in the P+RT group compared to RT alone group. Median time to local progression and median time to new bone metastases were advantageously delayed in the P+RT group. [Turk J Cancer 2002;32(2):57-65]

Key words: Bone metastases, pamidronate, radiation therapy

Radiation therapy (RT) has been considered as the treatment of choice for palliation of painful bone metastases for many years (1). It yields a pain relief rate of 80-90% and it prevents pathologic fractures as well as healing, with anticipated effect upon improving mobility and quality of life (2,3). However, patients frequently need re-treatment for newly apparent separate lesions and for recurring symptoms at the same site.

Pamidronate disodium (P), a second-generation bisphosphonate, binds tightly to bone hydroxyappetite and inhibits the resorption of bones with osteolytic metastases (4). The results of several open-label studies, which were mainly related with breast cancer, prostate cancer or multiple myeloma, suggest that using P alone or in combination with chemotherapy or hormoneotherapy relieves symptoms, improves the mobility and quality of life, reduces skeletal complications such as pathologic fractures, surgery to bone, need for analgesic or RT for pain, and delays time to disease progression in patients with lytic bone lesions (5-9). However, its role as a supplement to palliative RT in metastatic bone disease was not determined.

This prospective controlled study was conducted to determine whether adjunctive therapy with nine-months P administration could effectively improve

the efficacy of palliative RT, with regard to symptomatic relief, quality of life, sclerotic response of bone and time to local and distant progressive disease in patients with bone metastases.

Patients and Methods

Patients of 18 years of age or older with histologically proven primary cancers and radiologically confirmed bone metastases with at least one predominantly lytic lesion at least 1 cm in diameter, were enrolled into this prospective controlled study. All the patients had Eastern Cooperative Oncology Group (ECOG) scores for performance status of 0 to 2 at the time of enrollment and an estimated life expectancy of at least 3 months with no significant renal, hepatic or cardiac impairment, and gave oral informed consent. Treatment with RT, bisphosphonates, chemotherapy or hormonotherapy within 2 months before RT disqualified a patient from entering into the study. Treatment with chemotherapy or hormonotherapy after RT was allowed. RT was given in both groups with a total dose of 30 Gy of 3 Gy daily over 10 days. Co-60 or 6 MV and 10 MV photons from a linear accelerator were used with either single direction or parallel-opposed fields. For single posterior portal, the depth of the field was determined with anterior aspect of the vertebral body. Generally one vertebra above and below the known vertebral lesion was taken for treatment portals. In the combination group, 90 mg P (Aredia®; Novartis Pharma Inc, Basel, Switzerland) was given by an intravenous two-hour infusion in 250 ml of 5% dextrose or saline at the beginning of RT and it was repeated every four weeks for at least 9 cycles.

All patients were evaluated for bone pain, analgesic consumption, performance status, quality of life, tumor markers and bone mineralization parameters before treatment and percentage changes from base-line of these parameters were calculated 2, 6, 12, 24 and 36 weeks after RT. Radiographic surveys of the skeleton were performed during follow-up time. X-ray examinations of the involved region were performed before RT and every visits, bone scans before RT and then if necessary. Each patient was followed for survival until the patient's death or the last date of contact or lost to follow-up.

Bone pain was evaluated using a scoring system that quantified both severity and frequency of bone pain. Bone pain scores were calculated by multiplying the score for pain severity (graded from 0 to 3) by the score for pain frequency (graded from 0 to 3). A score of 0 indicates no bone pain, and a score of 9 indicates constant, severe bone pain. Analgesic use was assessed as a composite narcotic score obtained by multiplying a score for the type of medication administered by the frequency of administration of bone pain medication. A decrease in bone pain or analgesic scores represented an improvement. Infield progression at an irradiated bone is defined as the equal or greater level in sum of the pain and analgesic scores according to pre-treatment level. Performance status was evaluated according to standard ECOG criteria. Quality of life was determined using the EORTC-QLQC30 questionnaire. A central radiologist who was unaware of each patient's treatment regimen assessed the response of irradiated bone lesions and suspicious new metastases. Serum calcium (Ca) and serum alkaline phosphatase levels (ALP) were analyzed in all patients. As were serum levels of CA-15.3 and prostate-

specific antigen (PSA) in patients with breast cancer and prostate cancer, respectively. Bone mineral densities (BMD) of irradiated bone and lumbar spine (L2-4 vertebrae level) were measured by dual energy X-ray photon absorptiometry (DXA), using the Hologic QDR 2000 instrument (Hologic, Waltham, MA). BMD results were expressed in absolute values in standard deviation differences from age-matched normal (z score).

To compare parameter distributions we used either the Student's *t*-test or chi-square test. Percentage changes from base line in bone pain and analgesic scores, performance status, quality-of life index, serum tumor markers and bone mineralization parameters were compared between and in the groups by the Mann-Whitney-U and Wilcoxon rank-sum test, respectively. Kaplan-Meier estimates and log-rank test were used for comparisons of local and distant progression of bone disease. All tests were performed at an alpha error level of 0.05 (two sided).

Results

Between April 1998 and March 2000, 47 patients with bone metastases were treated with P+RT (19 patients) or RT alone (27 patients). Base-line characteristics of patients and treatment factors are listed in table 1 and are well balanced between the two groups for sex, age, ECOG performance status, primary tumor distribution, and primary sites of bone disease. Distribution of treatment machines and nominal portal area were also similar in two groups. Administrations of chemotherapy or hormonotherapy after RT were allowed particularly in patients with breast cancer (20), prostate cancer (7) and multiple myeloma (4). Specifically, there was no difference between the groups regarding percentage of patients treated with chemotherapy and/or hormonotherapy ($p=0.33$).

Mean changes in the symptomatic scores, quality of life index and bone mineralization parameters (% of base-line) are shown in table 2. In both groups, the patients had decreases from base line in bone pain during 24 weeks after RT, with no statistically significant difference between the two groups. At the 36th week, the pain scores were increased from base line in the RT group, whereas the P+RT group had decreasing bone pain scores (+25.0% vs. -42.6%, $p=0.05$). Similarly, analgesic scores improved from baseline during the 36 weeks of follow-up, without significant difference between the two groups. Quality of life scores also increased from baseline, with a significant difference between the two groups at 24th and 36th week, favouring the P group with improvements of 16% ($p=0.003$) and 21% ($p=0.001$), respectively.

More patients in the P+RT group had decreases in the levels of serum ALP than those in the RT group significantly at 24th week (-38.3% vs. -0.7%, $p=0.04$) and 36th week (-41.9% vs. +38.3%, $p=0.04$). During the study, there were no differences between the groups with regard to the changes of serum calcium and tumor marker levels.

In the 24th and 36th week of follow-up, changes in BMD of whole skeleton significantly increased from base line in the P group compared to the RT group (+9% vs. -1.7%; $p=0.02$ and +5.3% vs. -5.2%; $p=0.03$, respectively). In both groups, BMD of irradiated bone was improved from baseline, but the differences between two groups were not significant at each visit.

Table 1
Baseline patient characteristics and treatment factors

Characteristics	RT Alone (n = 28)	P+RT (n = 19)	P-value
Age (median)	54 (35-73)	51 (27-75)	0.30
Sex			
Male	14	6	0.21
Female	14	13	
ECOG performance status			
0-1	16	14	0.34
2	12	5	
Primary tumor			
Breast	13	10	0.71
Lung	4	1	
Myeloma	3	3	
Prostate	4	3	
Other	4	2	
Treatment site			
Vertebrae	14	8	0.85
Pelvis/hip	9	6	
Femur	3	5	
Humerus	2	0	
RT nominal portal area (cm ²)			
median	542	476	0.24
range	64-1888	73-980	
RT machine			
Co-60	24	15	0.59
Linac	4	4	
Systemic treatment			
None	5	6	0.28
Chemotherapy	14	7	0.26
Hormonotherapy	11	9	0.59
Combination	2	3	0.16

The median duration of follow-up was 43 weeks (range: 36-87) in the RT group and 61 weeks (range: 36-128) in the P+RT group. During follow-up, there were 5 patients with in-field progression (re-occurrence of pain) in the P+RT group and 14 in the RT group. New bone metastases were observed in five patients in the P+RT group and eight in the RT group. The proportion of patients who had in-field progressions or new bone metastasis were not significantly different between the two groups ($p=0.11$ and $p=0.95$, respectively, by χ^2 test).

The median time to local disease progression in irradiated bone was 36 weeks (95% CI, 27.8 to 44.3) for the P+RT group and 22 weeks (95% CI, 9.8 to 33.4) for the RT group (Log rank $p=0.152$). The median time to new distant bone metastasis was 51 weeks (95% CI, 15.7 to 56.3) for the P group vs. 35 weeks (95% CI, 35.7 to 36.3) for those receiving only RT (Log rank $p=0.039$).

Table 2
Changes from base-line over time between patients treated with radiotherapy alone (RT)
and those with pamidronate plus radiotherapy (P+RT)*

Parameters	Follow-up period after radiotherapy					
	6 weeks		24 weeks		36 weeks	
	RT	P+RT	RT	P+RT	RT	P+RT
Pain score	-33.4	-43.2	-1.5	-28.8	+25.0	-42.6
Interquartile range	-100/+100	-100/+100	-200/+200	-92/+300	-100/+100	-83/+100
p value		0.55		0.07		0.05
Analgesic score	-43.6	-53.4	-1.7	-38.3	+25.9	-38.8
Interquartile range	-100/+100	-100/0	-100/+200	-100/0	-100/+300	-100/0
p value		0.58		0.44		0.09
Quality of life index	+8.6	+12.0	-1.1	+16.3	-0.7	+21.3
Interquartile range	-45/+49	-6/+42	-45/+50	-7/+48	-12/+10	+6/+57
p value		0.28		0.003		0.002
Serum calcium	0	-1.8	+2.0	-4.0	+0.4	-3.4
Interquartile range	-12/+19	-31/+16	-17/+53	-11/+7	-11/+7	-11/+5
p value		0.42		0.24		0.14
Serum ALP	+7.8	-13.1	-0.7	-38.3	+38.3	-41.9
Interquartile range	-61/+288	-70/+141	-70/+122	-81/+74	-43/+253	-80/+8
p value		0.19		0.04		0.04
Serum tumour marker	+10.0	+9.5	-40.4	-4.8	+14.9	-55.7
Interquartile range	-69/+240	-85/+126	-94/+48	-100/+179	-83/+100	-100/0
p value		0.92		0.34		0.06
BMD irradiated bone	+1.5	+2.6	+25.9	+34.8	+48.5	+42.3
Interquartile range	-15/+11	-2/+15	-23/+200	-2/+186	+2/+250	+4/+186
p value		0.92		0.24		0.46
BMD whole skeleton	+5.4	+5.1	-1.7	+9.0	-5.2	+5.3
Interquartile range	-5/+24	+1/+20	-8/+8	-3/+31	-7/-2	-8/+15
p value		0.62		0.02		0.03

*Mean values (% of baseline), interquartile ranges and p values are shown

Discussion

Several open-label studies of P in the treatment of bone metastases have reported results favouring P therapy given in combination with conventional systemic anticancer therapy, compared with conventional systemic therapy alone (5-9). However, its role as a supplement to local irradiation in metastatic bone disease is not well established.

In a large randomized study of Theriault et al. (6), P infusions significantly reduced the rates of bone pain (60% vs. 35%), analgesic need (74% vs. 60%), and decreased mean analgesic scores from base-line (+0.7 vs. +1.55, $p=0.009$) compared to placebo in patients with stage IV breast cancer who received chemotherapy. In a non-randomised high dose, 120 mg P study, significant improvement in quality of life (+8%) was found at six weeks after therapy (7). In our study, monthly infusion P supplement to RT significantly decreased pain scores and improved the quality of life, which is consistent with studies above. Surprisingly, we could not observe any significant difference between two groups as to the analgesic score changes during follow-up. A major, but insignificant difference was observed at 36th week with a mean 38.8% decrease in the P+RT group and 25.9% increase in the RT group ($p=0.09$). Similarly, in a large randomised study from Sweden, statistically insignificant consumption of opioid analgesics was observed in breast carcinoma patients with bone metastasis, as the dose used in this study (60 mg I.V., per 4 weeks) was lower than ours (10).

Currently, varieties of biochemical markers regarding bone resorption are under investigation (11). Some have been correlated with, but not shown to be statistically significant predictors of prognosis or response. In our study, a significant decrease in serum ALP levels, which might be a useful systemic marker of bone formation, in the P+RT group compared to RT alone (-38.3% vs. -0.7%) and (-41.9% vs. +38.3%) was observed after 24 and 36 weeks, respectively. A similar pattern of ALP levels between baseline and last measurements (-29% for the P plus chemotherapy group vs. +9% for the chemotherapy alone group) was reported in metastatic patients with breast cancer, who were followed by a median of 11 months (5). Contrary to a study which reported a significant fall in serum calcium levels (median 2.51 to 2.40) six months after P treatment, we could not observe any significant difference between two groups in terms of changes in the calcium levels from base-line during follow-up (12).

In the literature, the effects of P supplementation to conventional cancer treatment on tumor marker levels have not been fully investigated. We did not observe any significant changes in the CA 15.3 levels of 20 patients with breast cancer or in the PSA levels of six patients during the study.

The effects of using bisphosphonates in combination with conventional cancer treatments on BMD levels were studied only for clodronate, another bisphosphonate, which resulted in significant increases in BMD of the whole skeleton in patients with osteoporosis and bone metastasis as in our results (13,14). It is well known that external irradiation produces some healing and reossification in nearly 8% of lytic lesions in unfractured bone (15). In a study, a significant increase in BMD of osteolytic metastases, and a significant decrease in osteosclerotic metastases six weeks after RT were found by using

quantitative CT measurements (16). During our study, BMD of irradiated bones was improved in both groups, with an insignificant difference between the two groups and the most important improvement was observed at 36 weeks (+42.5% in the P+RT group and +48.5% in the RT alone group).

The preclinical observations suggest that a benefit in reduction of tumor burden in bone metastases and possibly at other metastatic sites may occur when P is used in the adjuvant setting, with a resulting improvement in local and distant disease free survival (17,18). In a randomized study of Hortobagyi *et al* (5), a significantly delayed median time to the local and distant progression was reported in breast carcinoma patients with bone metastasis (13.9 vs. 7.0 months, $p=0.001$). According to two large randomised studies, the addition of P to hormone therapy in patients with breast cancer or chemotherapy in patients with multiple myeloma lowered the proportion of skeletal events (pathologic fractures, surgery to bone, need for analgesics or RT for pain and new bone metastasis) (56% vs. 67% and 38% vs. 51, respectively) compared to placebo (6,8). These findings were also confirmed by further follow-up results regarding the effects of long-term (up to 24 months) treatment (19). Our results of the time to in-field progression (36 weeks vs. 22 weeks) and new metastasis (51 weeks vs. 35 weeks), favouring P supplementation to palliative RT, co-incide with the results of those reported studies.

Except from a small, non-randomised study, there is no sufficient data regarding to support a role for P as an adjunctive therapy to RT in patients with pain caused by metastatic bone disease when systemic chemotherapy and/or hormone therapy is not being used (20). Merely, the data related to the clodronate is available in this setting (21,22). Caristi *et al.* (21) demonstrated a significant improvement in the pain relief in patients treated with clodronate plus RT compared to RT alone (66% and 58%, respectively). In the study of Botturi *et al.* (22), a marked protective effect of this drug on both local disease progression and appearance of new lytic areas were observed. Results of our study, which used P, are also consistent with those clodronate studies.

In some randomized studies of palliative RT, the frequency of pain relief ranged from 40% to 90%, and median duration of minimal relief ranged from 11 to 29 weeks, mostly independent of dose (3,15). In our study, median duration of relief was similar (22 weeks) to those studies in which patients were treated with only RT, whereas studies in which patients were treated with P and RT was superior (36 weeks) to those studies due to the marked benefit of P administration.

Data from retrospective studies and prospective randomized trials showed that palliative RT of bone metastasis with single fraction might be as effective as multifraction regimens (23-26). Although there was no significant difference in pain relief, patients receiving a single fraction were more likely to have the same site re-irradiated, whereas more patients treated with fractionated RT tended to be re-treated with analgesics. Based on the results of our study, we believe that the supplementation of P to the palliative RT may improve particularly the results of single fraction RT, which may be advantageous for both patients and institutions.

Despite the small sample sized basis of our study, we may conclude that monthly infusions of P is an effective supplement to improve the RT results regarding pain relief, quality of life, bone mineralization of whole skeleton, local

progression free interval for irradiated bones and distant metastasis free interval, significantly 24 weeks after therapy in patients with predominantly lytic bone lesions due to metastatic cancer. We believe that, it is necessary to perform double-blinded multicenter randomised studies with more patients in this setting. Comparing single dose RT plus P with conventional palliative RT alone or comparing P with new potent bisphosphonates such as zoledronic acid in combination with palliative RT may be other directions for future research.

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